Simian Virus 40 (SV40), Polio Vaccine, and Cancer

Q & A

At a glance: SV40 is a virus found in some species of monkey. Soon after its discovery in 1960, SV40 was found in polio vaccine.
Over 98 million Americans received one or more doses of polio vaccine during the period (1955-1963) when some of the vaccine was contaminated with SV40. SV40 has been found in certain types of human cancers, but it has not been determined that SV40 causes these cancers. The majority of evidence suggests there is no causal relationship between receipt of SV40-contaminated vaccine and cancer; however, some research results are conflicting and more studies are needed.

1. **What is SV40?**

   Simian virus 40, or SV40, was discovered in 1960. It occurs naturally in some species of monkeys, though it does not typically cause symptoms or illness except in cases where the animal has chronic problems with its immune system (Shah and Nathanson, 1976). In those cases, the animals develop lesions associated with SV40 in their kidneys and brains (Newman et al., 1998).

   SV40 is not related to HIV, the virus that causes AIDS in humans, or to simian immunodeficiency virus (SIV), the virus that causes an AIDS-like disease in some monkey species.

2. **Why is there so much interest in SV40?**

   Soon after its discovery in 1960, SV40 was identified in polio vaccine. It was found in the injected form of the vaccine (IPV), not the kind given by mouth (OPV). At that time, rhesus monkey kidney cells, which contain SV40 if the animal is infected, were used in preparing viral vaccines. Because SV40 was not discovered until 1960, no one was aware that polio vaccine made in the 1950s could be contaminated. In 1961, the virus was found to cause tumors in rodents (Eddy et al., 1961). That same year, the federal government required that new stocks of polio vaccine be free of SV40. However, existing polio vaccine stocks were not recalled and were used until 1963. When SV40 was discovered, researchers did not know if the virus could negatively affect people's health. Many viruses that harm animals have no effect on people because of the biological differences between animals and humans.

   Interest in SV40 has increased in the last several years because the virus was found in certain forms of cancer in humans, for instance mesotheliomas (rare tumors located in the lungs), brain, and bone tumors (Carbone et al., 1994; Jasani

et al., 2001). More recently, SV40 has also been found to be associated with some types of non-Hodgkin's lymphoma (Shivapurkar et al., 2002; Vilchez et al., 2002).

3. **Does polio vaccine being given in the U.S. today contain SV40?**

   No, polio vaccines being used today do not contain SV40.

   - SV40 was completely removed from the seed strains of the vaccine viruses in the early 1960s.
   - The polio vaccine currently used in the U.S. (inactivated polio vaccine, or IPV) is no longer prepared in primary rhesus monkey kidney cells. It is produced in human or African green monkey cell lines that have been extensively tested for contaminants, including SV40.
   - The poliovirus used in IPV is killed with formaldehyde. This procedure also kills viral contaminants, such as SV40. Formaldehyde was also used in the SV40-contaminated vaccine, but in 1961 researchers found that the process killed 99.99% of SV40 and 1 in 10,000 SV40 particles survived (Hilleman, 1998).
   - Today's testing methods are better. Any live SV40 would be detected by these methods.

4. **What about concerns that the testing methods used to screen oral polio vaccines could have missed certain strains of SV40?**

   Oral polio vaccine (OPV, which is no longer recommended for use in the U.S. but is used elsewhere in the world) differs from IPV because it contains weakened, rather than killed, poliovirus. Because it is a live vaccine, formaldehyde or other inactivation agents were not used in producing OPV. The poliovirus that was used to produce OPV was grown on monkey kidney cells. Screening for SV40 in the monkey kidney cells used to produce OPV was implemented in the early 1960s after the virus was first discovered. Manufacturers also treated the stocks of weakened poliovirus in order to remove any SV40 that might have been present in them.

   A study (Rizzo et al., 1999) raised concern that some lots of OPV may have been contaminated with a slow-growing SV40 strain that would not have been detected with the methods used to test it. However, this study did not follow the actual testing protocol used to ensure that vaccine is free of SV40. Subsequent studies (Minor et al., 2001) confirmed studies from the early 1960s (Melnick) showing that the testing methods used were sufficient to detect even slower-growing strains of SV40. In addition, researchers from the FDA used the very sensitive polymerase chain reaction (PCR) methodology to search for SV40 DNA in OPV manufactured in the U.S. between 1972 and 1996 (the FDA only tested vaccines produced as far back as 1972, because there were no existing lots of OPV at FDA that were produced between 1962 and 1972). SV40 DNA sequences were not found in any of the vaccine lots tested (Sierra Honigmann & Krause, 2000). OPV

is no longer produced in the U.S.; if production were to be resumed, it would continue to be under extremely strict conditions that eliminate the possibility of any contamination with SV40.

5. **Who received SV40 contaminated polio vaccine in the U.S.?**

   Over 98 million Americans received one or more doses of IPV (the injected form of the polio vaccine) during the period (1955-1963) when some of the vaccine was contaminated with SV40. However, not all doses of IPV were contaminated. It has been estimated that 10-30 million of the 98 million people who received a polio shot actually received a vaccine that contained SV40 (Shah and Nathanson, 1976). In addition, about 10,000 volunteers who received an experimental oral polio vaccine (OPV) between 1959-1961 may have been exposed to SV40 (the vaccine was later licensed in 1963, subsequent to SV40 removal from the seed stock). All of the evidence to date indicates that after 1963, all vaccines on the U.S. market were free of SV40.

6. **Were any other people in the United States possibly exposed to SV40-contaminated vaccines?**

   Yes. SV40 was a contaminant of respiratory syncytial virus given to a few volunteers in an experimental study of infection with the live virus (Shah and Nathanson, 1976). In addition, SV40 was also found in adenovirus vaccines given to more than 100,000 young men in army camps in the 1950s and 1960s to protect them from respiratory infections (Sherwood et al., 1961).

7. **Is receiving contaminated vaccine the only way to become infected with SV40? Does it spread from person-to-person?**

   Receiving contaminated vaccine is not the only way to become infected with SV40. Data suggest that SV40 has infected a small percentage of the human population independently of the polio vaccine. A study of German medical students found that 12% had SV40 antibodies in 1952, before the introduction of the polio vaccine (Geissler et al., 1985). Moreover, SV40 has been identified in people born in the 1980's and 1990's, well after the elimination of SV40 contamination from polio vaccines. This has led some to consider that the virus may spread from person-to-person. Some laboratory workers may have been exposed to SV40 (Horvath, 1965). It is not known whether people who live in countries with wild rhesus monkeys also could be exposed to SV40. Exactly how SV40 is transmitted among humans and how common it is among people in the U.S. population are unknown.

8. **SV40 is known to cause tumors in rodents. Have research studies found an association between SV40 and cancer in humans?**

Yes. An association has been found between SV40 and certain types of cancer in humans. However, though the virus or its DNA have been found in certain types of cancer, it has not been determined that SV40 causes these cancers. Finding that two events are "associated" is not the same as establishing that one event caused the other.

SV40 was linked with mesothelioma after tumors developed in hamsters that were injected with SV40 into the lungs, heart and abdomen (Cicala et al., 1993). Mesotheliomas are rare cancers usually located in the lining of the lungs in humans and are associated with asbestos exposure. SV40 has been found in 47% to 83% of human mesothelioma tumors (Carbone, 1999). In addition, reports have documented an association between SV40 and brain and bone tumors (Jasani, 2001).

Two recent studies also found an association between SV40 and non-Hodgkin's lymphoma (Shivapurkar et al., 2002; Vilchez et al., 2002). These studies identified the virus in 42-43 percent of non-Hodgkin's tumors, while finding no SV40 in tissue from healthy study volunteers. Lymphoma is a general word for cancers that develop in the lymphatic system – the tissues and organs that produce, store and carry white blood cells that fight infection and other diseases. Hodgkin's disease is one type of lymphoma; all others are called non-Hodgkin's lymphoma. Lymphomas account for about 5 percent of all cases of cancer in this country (http://www.nci.nih.gov).

9. **What steps have been taken by the government to see if SV40-contaminated vaccines affected people's health?**

When SV40 was discovered in 1960, researchers did not know if the virus could negatively affect health. Many viruses that harm animals have no effect on people because of the biological differences between animals and humans. However, to investigate the possibility, several federally funded studies were carried out during the 1960s, 1970s and 1980s to follow persons who received polio vaccines (the results from some of these studies are discussed below). In addition, on January 27-28, 1997, the U.S. Food and Drug Administration, the Centers for Disease Control and Prevention, the National Institutes of Health, and the National Vaccine Program Office sponsored an open public meeting with scientists and physicians to discuss research findings on SV40. At the meeting they discussed available data and determined that further research into the field of SV40 was needed (Brown & Lewis, 1998). To learn how to order the proceedings of this meeting, go to: http://www.karger.ch/bookseries/debis/debis094.htm

In 2001, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) asked the National Academy of Sciences' Institute of Medicine (IOM) to establish an independent expert committee to review hypotheses about existing and emerging immunization safety concerns. These reviews involve an assessment of factors such as the biologic mechanisms of the

hypothesis, alternative hypotheses, as well as the available scientific evidence to date. In 2002, the IOM Immunization Safety Review Committee will examine the existing scientific data on SV40-contaminated polio vaccine and cancer. Upon completion of their review, the committee will produce a report with recommendations regarding research, policy review, and communications at: www.iom.edu/IOM/IOMHome.nsf/Pages/immunization+safety+review.

10. **What has research found regarding the health affects of receiving SV40-contaminated vaccine? Has there been an increase in cancer among people who received SV40-contaminated polio vaccine?**

    The majority of evidence suggests there is no causal relationship between receipt of SV40-contaminated polio vaccine and cancer development; however, some research results in this area are conflicting and more studies are needed.

    Since the discovery of SV40, several studies have been done to compare cancer rates in groups of individuals known or strongly presumed to have received SV40-contaminated polio vaccine to rates in persons known or strongly presumed not to have received SV40-contaminated vaccine. A brief description of some of these studies follows:

    - Two studies (De Rienzo et al., 2002; Emri et al., 2000) examined mesothelioma tissue from a small number of patients in Turkey, where SV40-contaminated vaccines were not used, and found no SV40. The researchers also examined mesothelioma tissue from a small number of patients in the US and Italy, where SV40-contaminated polio vaccines were used, and found SV40 in some of the specimens.

    - In 1999, Fisher and colleagues reported increased rates of ependymomas, osteogenic sarcomas, other bone tumors, and mesotheliomas among people who were potentially exposed to SV40-contaminated polio vaccine. However, the number of cases in this study was too small to draw any statistically valid conclusions.

    - In 1998, the National Cancer Institute published findings from a study (Strickler et al., 1998) that revealed that, after 30 years, there was no increased incidence of cancer in persons who may have received vaccine containing SV40. The study used the National Cancer Institute's SEER database, which contains information on more than 2.5 million cancer cases in the U.S., and the Connecticut Tumor Registry, and included millions of people exposed to contaminated poliovirus vaccine and decades of cancer incidence and mortality data. Comparisons of the rates of cancer were made between persons who had received SV40-contaminated vaccine as infants born in 1956-1962 and persons born in 1947-1952 and 1964-1969. This study looked specifically for types of rare cancers that have been found to contain SV40 in recent cellular research

(Carbone et al., 1994) and found no significant increased incidence compared with persons who had not received contaminated SV40 vaccine. The rare cancers included ependymomas (cancer of cells found in developing fetal neural tubes from which the brain and spinal cord arise as a baby develops), osteosarcomas (a type of bone cancer), mesotheliomas (a type of cancer that originates in the tissue lining of the lung cavity) and brain cancers.

- Olin et al. (1998), conducted a long-term follow-up study of 700,000 people in Sweden who received polio vaccine potentially contaminated with SV40 in 1957 as school-age children. Their results revealed no increased cancer incidence between persons who received vaccine containing SV40 and those who did not.

- Geissler (1988) analyzed German National Cancer Registry data to compare the incidence of cancer in 885,783 persons born between 1959-1961 who received polio vaccine that may have been contaminated with SV40 and compared it with 891,321 persons born between 1962-1964 who received SV40 free vaccine. These data demonstrated that persons who received polio vaccine possibly contaminated with SV40 did not develop more tumors within a 20-year period than did those who received vaccine that did not contain SV40.

- Mortimer (1981) studied cancer deaths of 1073 persons born between 1960-1962 who received oral poliovirus or inactivated poliovirus vaccine that contained SV40 when newborn. The follow-up study over 17-19 years revealed no increased number of deaths from cancer. In 2001, a thirty-five year follow-up study of this group was published. The study found no deaths in the group due to tumors of the type that have been associated with SV40 (Carroll-Pankhurst, 2001).

- Fraumeni et al. (1970) followed 1000 persons who had received SV40 contaminated poliovirus vaccine within a few days after birth. The majority of these people received the SV40-contaminated oral vaccine. At eight years of age, no cancer deaths were identified in the exposed group.

- Fraumeni et al. (1963) focused on a cohort of children age 6-8 years who received inactivated poliovirus vaccine in 1955. A comparison was made based on whether children received vaccine with high, low or no detectable amount of SV40 contamination. Mortality rates from leukemia and all other cancers from 1950-1959 were compared across the three groups. No differences in cancer rates were found for this period.

In summary, the majority of studies in the U.S. and Europe that compare persons known or strongly presumed to have received SV40-contaminated polio vaccine with those known or strongly presumed not to have received SV40- contaminated

polio vaccine have not shown a causal relationship between receipt of SV40-contaminated polio vaccine and cancer. It should be noted, however, that SV40 infection has been found in persons who did not receive SV40-contaminated polio vaccine and that for some study participants it cannot be known with certainty whether or not they received SV40-contaminated vaccine. Because of this, there may be errors in these studies that make it harder to detect a true increased cancer risk associated with receipt of SV40-contaminated polio vaccine. In addition, research is needed that focuses on the long-term consequences of SV40 exposure, as some cancers like mesotheliomas typically occur later in life and would not have been detected in several of the studies described above. Moreover, additional studies are needed which focus on the potential long-term effect of SV40 exposure on health outcomes other than cancer (Strickler and Goedert, 1998). Because the CDC takes this issue very seriously, the agency has asked an expert committee (described in question 9) to review the existing data on this topic and provide recommendations for future research.

11. **Have research studies looked at the risk of cancer in children whose mothers received SV40-contaminated polio vaccine?**

    Yes, two studies concerning maternal vaccination with SV40-contaminated vaccines and risk of cancer in offspring have been conducted. Each study reported an association.

    1. Heinonen et al. (1973) reported a higher incidence of neural malignancies in children born to mothers who received inactivated poliovirus during pregnancy. The prospective study of over 50,000 women who were pregnant between 1959-1965 identified 24 malignancies in their children during the first 4 years of life. The rate of malignancy was about two-fold greater in children born to mothers immunized during pregnancy when compared with children born to unimmunized mothers or mothers who received influenza or OPV vaccines. Neural tumors accounted for most of the difference.

    2. Farwell et al. (1979) found that of 15 cases of medulloblastoma in children born in Connecticut between 1956-1962, 10 were born to mothers exposed to SV40 contaminated polio vaccine while 5 were born to mothers unexposed. Interpretation of these results, however, is hampered by the low response rates and uncertain accuracy of vaccination histories by obstetricians (Strickler et al., 1998).

    Additional studies are needed that focus on maternal vaccination with SV40-contaminated vaccines and risk of cancer and other health effects in offspring.

12. **If I have one of these cancers does it mean that SV40 caused it?**

No. The possible role of SV40 in human cancers is not fully understood and is the topic of continued research.

13. **Can I obtain a test to see if I am infected with SV40?**

    Blood tests can identify if a person has antibodies to SV40, but there is no test for SV40 commercially available at this time.

    Research laboratories are currently refining the techniques used to detect SV40. PCR (polymerase chain reaction) assays are currently in use to detect SV40 DNA segments. Because of inconsistent results between laboratories, there is a need to develop a standard PCR assay (Levine et al., 1998).

14. **What should I do if I received polio vaccine during 1955- 1963?**

    There are no recommended treatments or tests for persons that may have been exposed to SV40. If you have concerns about your health, please make an appointment to see your health care provider.

15. **Where can I get more information about SV40?**

    The Food and Drug Administration has been the federal government lead agency in answering questions relating to SV40 in polio vaccine. You may call the FDA at the following number: 1-800-835-4709.

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